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Heterogeneity in reporting venous thromboembolic phenotypes in COVID-19: Methodological issues and clinical implications

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Abstract

COVID-19 is associated with increased risk of venous thromboembolic events (VTE). However, there is significant heterogeneity in the thromboembolic phenotypes of COVID-19 patients (deep vein thrombosis, pulmonary embolism/thrombosis). The latter might be partly attributed to the variation in VTE risk factors in COVID-19 patients including: (i) patients' characteristics; (ii) hospitalization conditions and interventions; (iii) SARS-Cov-2 specific factors (coagulopathy, endothelial injury/microthrombosis). Furthermore, there is methodological heterogeneity in relation to the assessment of VTE (indications for screening, diagnostic methodology, etc). Physicians should be aware of the increased VTE risk, strongly consider VTE screening, and use thromboprophylaxis in all hospitalized patients.

Keywords: SARS-CoV-2; pulmonary embolism; deep vein thrombosis; prevalence

Accumulating evidence suggests that severe coronavirus disease 2019 (COVID-19) is associated with an increased venous thromboembolic risk.[1,2] It appears that SARS-CoV-2 in severe cases induces an excessive immune response associated with cytokine storm leading in turn to coagulation disorders.[1.2] The latter can be observed at both local level with lung endothelial injury and microthothrombosis, as well as at systematic level with disseminated intravascular coagulopathy.[1,2]

In light of the emerging evidence on the thromboembolic risk in COVID-19, recent publications highlight 2 important issues: First the high rate of venous thromboembolism events (VTE) in COVID-19 patients, and second the variety of the observed thromboembolic phenotypes. Indeed, 11 recent studies reported both the prevalence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in COVID-19 patients with prevalence numbers ranging from 0% to as high as 54% (**Table 1**).[3-13] Importantly, there was no consistent relationship between the reported prevalence of DVT and PE. **It should be mentioned that most studies have included mainly patients in intensive care unit (ICU) who presumably had severe COVID-19 (Table 1). One study reported that the prevalence of VTE was significantly higher in ICU versus general ward patients (47% and 3% respectively).[6]**

These data indicate that there is heterogeneity in the reported VTE risk – although recognized by all as increased - as well as in the thromboembolic phenotypes of COVID-19 patients (isolated DVT, isolated pulmonary embolism/thrombosis, concurrent DVT and pulmonary embolism/thrombosis). It might be suggested that variation in several VTE risk factors in COVID-19 patients accounts for this observed heterogeneity which are presented in **Figure 1** and include: (i) characteristics of the patients including well-established risk factors for VTE; (ii) hospitalization conditions and interventions; (iii) SARS-Cov-2 specific factors.

Further to the above, an additional important issue is the heterogeneity in the methodology used across studies to identify VTE in COVID-19 patients. Indeed, factors that might play a role include: (i) indications for VTE screening; i.e. consecutive patients or selected ones upon clinical (respiratory or hemodynamic deterioration) or biochemical (increase in d-dimer values) suspicion, and (ii) the diagnostic methodology applied i.e. ultrasonography or computed tomography

pulmonary angiography or both, which is largely dependent on the available human and equipment resources.

Interestingly, even in studies which reported screening for DVT with leg compression ultrasonography in all their patients, there has been significant heterogeneity. Specifically, Ren et al reported that among 48 critically ill COVID-19 patients hospitalized in the ICU, 41 (85%) presented with lower extremity DVT, mainly in the pattern of isolated distal DVT.[14] On the contrary, in another study in 64 COVID-19 patients hospitalized in general ward, none was found with DVT.[15] The two studies included patients with similar age (median 70 years) and gender distribution, yet the former study included patients admitted in ICU with a more severe disease and 7-fold higher d-dimer levels.[14,15] It should be mentioned that thromboprophylaxis was administered in both studies.[14,15]

The role of the d-dimer assessment and of optimal thromboprophylaxis in COVID-19 patients is of paramount importance. Some studies have shown that increased d-dimer predict the development of VTE.[3,6,9] Thus, patients with increased d-dimer values on admission or increasing d-dimer values during their hospitalization should be candidates for VTE screening. Moreover, several societies now recommend the use of thromboprophylaxis in all hospitalized patients.[1] Although prophylactic dosing is generally recommended, some experts consider the use of intermediate dosing but relevant studies are lacking.

In summary, and in terms of clinical practice, physicians dealing with COVID-19 patients should be aware that: (i) The risk of venous thromboembolism is high, yet with variable incidence of phenotypes (DVT and PE); (ii) All hospitalized patients require thromboprophylaxis, yet the optimal dosing is uncertain; (iii) VTE screening should be strongly considered and influenced by clinical and biochemical characteristics (d-dimer).

Authors' contributions

AK and KGK performed the research and drafted the manuscript
GSG, KS provided critical review and supervision

Table 1. Main characteristics and findings of studies.

Study	Setting	N	Age, ys ±SD (range)	Males (%)	Prevalence of DM/CVD/PD (%)	Median (range) SOFA/PaO_2/FiO_2	Antithrombotic treatment dosing	Prevalence of DVT/PE (%)	d-dimer (µg/ml; median values) and predictive value (ratio and 95% CI)
Stoneham et al.[3]	General ward	274	VTE 67±12	VTE 67	VTE 38/29/38	NR	NR	2/6	VTE vs nonVTE: 4.1 vs 1.2 Adjusted OR for VTE: 1.4 (1.2,1.8)
Wright et al.[4]	ICU	44	54 (19-86)	64	41/NR/14	8 (7-10)/163 (127-235)	Prophylactic	25/0	1.8 (0.9-4.1)
Thomas et al.[5]	ICU	63	59±13	69	NR	NR	Prophylactic	2/8	0.4 (0.1-3.6)
Middeldorp et al.[6]	General ward 62%; ICU 38%	198	61±14	66	NR	NR	Mainly prophylactic	13/7	VTE vs nonVTE: 2.6 vs 1.0 Subhazard ratio for VTE: 1.4 (1.1,1.9)
Helms et al.[7]	ICU	150	63 (53-71)	81	20/48/14	8 (5-10)/125 (97-170)	Mainly prophylactic	2/17	2.3 (1.2-20.0)
Lodigiani et al.[8]	General ward 84%; ICU 16%	388	66 (55-85)	68	23/33/9	NR	Mixed doses	2/3	Rapid increase in d-dimer in non-survivors
Poissy et al.[9]	ICU	107	PE 57 (29-80)	PE 59	NR	PE 4 (0-4)/NR	Prophylactic	5/21	Subhazard ratio for PE: 1.8 (1.0,3.2)
Tavazzi et al.[10]	ICU	54	VTE 68±7	NR	NR	NR	Prophylactic	15/6	NR
Llitjos et al.[11]	ICU	26	68 (52-75)	77	NR	3 (2-5)/87 (74-116)	Mainly therapeutic	54/23	1.8 (1.1-2.9)

Beun et al.[12]	ICU	75	NR	NR	NR	NR	NR	4/27	NR
Klok et al.[13]	ICU	184	64±12	76	NR	NR	Mainly prophylactic	2/35	NR

CVD, cardiovascular disease; DM, diabetes mellitus; DVT, deep vein thrombosis; ICU, intensive care unit; NR, not reported; OR, odds ratio; PD, pulmonary disease; PE, pulmonary embolism; SOFA, Sequential Organ Failure Assessment; VTE, venous thromboembolism

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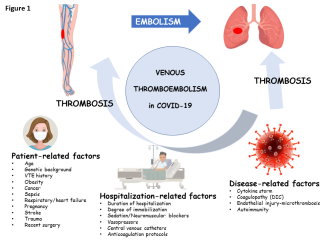
Figure 1. Factors increasing the venous thromboembolism risk in COVID-19.



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